REMARKS

Prior to this Response, claims 1-18 were pending in this application. Claims 1, 7, 9, 15, and 17 have been amended. The Specification has been amended to remove references to the trademark "Avandia".

The amendments do not introduce new matter within the meaning of 35 U.S.C. §132. Basis for the claim amendments is found on page 8, lines 23-24; in claims 1-18 as originally filed; and elsewhere throughout the specification and claims. Accordingly, entry of the amendments is respectfully requested.

1. Objection to the Specification

The Office Action objects to the Specification for the following reasons:

> The attempt to incorporate subject matter into this application by reference to the non-patent literature references and U.S. patents, on page 1, lines 9-22, is improper because information submitted for consideration must be filed as an information disclosurement statement.
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> The use of the trademark AVANDIA TM has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.
>
> Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks. It is suggested that each letter of the trademark be capitalized or include a proper trademark symbol, such as TM or ®.

Applicants thank the Examiner for her helpful comments. Applicants have amended the Specification and claims to remove references to the trademark "Avandia". Further, an Information Disclosure Statement is filed herewith.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the objections to the Specification.

2. Rejection of Claims 7, 9, 15, and 17 under 35 U.S.C. §112, second paragraph

The Office Action rejects claims 7, 9, 15, and 17 under 35 U.S.C. §112, second paragraph, for the following reasons:

> Claims 9 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
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> Claims 9 and 17 recite the phrase "wherein said algae is *Dunaliella bardawil*". The verb does not agree with its subject in number. Applicant may overcome the rejection by replacing "algae" with alga.
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> Claims 7 and 15 are rendered vague and indefinite by the trademark term "AVANDIA ™".

The foregoing claim amendments obviate these rejections. In particular, Applicants have amended claims 7, 9, 15 and 17 to replace the term "algae" in claims 9 and 17 with "*Dunaliella*" and remove the trademark "Avandia".

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

3. Rejection of Claims 1, 2, 8-10, and 16-17 under 35 U.S.C. §102(b)

A. The Office Action rejects claims 1 and 8-10 under 35 U.S.C. §102(b) as being anticipated by Levy, et al. (U). As the basis for this rejection, the Office Action states:

> Applicant claims a method for treating a disease selected from diabetes mellitus and atherosclerosis comprising administrating to a subject an effective amount of crude Dunaliella powder. Applicant claims the method according to Claim 1, wherein said crude Dunaliella powder is administered orally. Applicant further claims the method according to Claim 1, wherein said algae is Dunaliella bardawil. Applicant further claims the method according to Claim 1, wherein said powder is encapsulated.
>
> Levy teaches a method of treating patients suffering from diabetes mellitus and at high risk of developing atherosclerosis comprising administering an effective amount of an extract obtained from Dunaliella bardawil in encapsulated form. Levy teaches that the administration of the algal extract inhibited the oxidation of LDL derived from diabetic patients.

Claim 1 has been amended to define the *Dunaliella* powder as comprising an approximately 1:1 ratio of all-trans and 9-cis β-carotene. Claims 8-10 depend from claim 1 and therefore include the new limitation. Levy does not teach the use of *Dunaliella* powder comprising an approximately 1:1 ratio of all-trans and 9-cis β-carotene. Therefore, Levy does not anticipate the claims as amended.

B. The Office Action rejects claims 2, 16 and 17 under 35 U.S.C. §102(b) as being anticipated by Takahashi, et al. (V). As

the basis for this rejection, the Office Action states:

> Applicant claims a method for reducing triglycerides and/or increasing HDL cholesterol levels in the plasma of a subject comprising administrating to the subject an effective amount of crude Dunaliella powder. Applicant claims the method according to Claim 2, wherein said crude Dunaliella powder is administered orally. Applicant further claims the method according to Claim 2, wherein said alga is Dunaliella bardawil.
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> Takahashi teaches that the administration of an effective amount of a powdered extract of Dunaliella bardawil to hypercholesterolemic mice significantly decreased the levels of plasma total cholesterol and LDL-cholesterol.

Applicants respectfully traverse these rejections on the basis that Takahashi, et al. fails to teach the claimed subject matter. Applicants' claims as presently amended are directed to a method for reducing triglycerides and/or increasing HDL cholesterol levels in the plasma of a subject by administrating to the subject an effective amount of crude *Dunaliella* powder.

By contrast, Takahashi, et al. disclose that *Dunaliella* decreases the levels of plasma total cholesterol and LDL cholesterol in hypercholesterolemic mice.

To constitute anticipation under 35 U.S.C. § 102, all material elements of a claim must be found in one prior art source. In re Marshall, 577 F.2d 301, 198 USPQ 344 (CCPA 1978); In re Kalm, 378 F.2d 959, 154 USPQ 10 (CCPA 1967). Takahashi, et al. also teach that *Dunaliella* extract increased or did not affect the level of plasma triglyceride, and decreased HDL-cholesterol. This teaching

is in direct opposition to claim 2, which claims a method for reducing triglycerides and/or increasing HDL cholesterol levels in the plasma of a subject by administrating to the subject an effective amount of crude *Dunaliella* powder. Thus, not only does Takahashi, et al. not teach the inventive subject matter, but it in fact teaches away. Thus, in the absence of any teaching in Takahashi, et al. that *Dunaliella* extract reduces triglycerides and/or increases HDL cholesterol levels in the plasma of a subject, Takahashi, et al. does not anticipate the present claims.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

4. Rejection of Claims 1, 3-15 under 35 U.S.C. §103(a)

A. The Office Action rejects claims 1 and 8-10 under 35 U.S.C. §103(a) as being unpatentable over Levy, et al. (U) and Levy, et al. (W). As the basis for this rejection, the Office states:

> The teachings of Levy (U) were set forth above. Levy does not expressly teach a method of treating a disease wherein the disease is atherosclerosis. However, it would have been obvious to one ordinary skill in the art at the time the invention was made to use the method taught by Levy to provide the claimed invention because at the time the invention was made it was well known in the art of medicine that atherogenesis involves oxidative modification of low-density lipoprotein and that accelerated atherosclerosis is common in patients with diabetes mellitus, as evidenced by the teachings of Levy (U) set forth above; and, that atherogenesis involves oxidative modification of low-density lipoprotein (LDL), as evidenced by the teachings of Levy (W). Firstly, Levy

(U) teaches orally administering 60 mg/day of a beta-carotene containing extract of Dunaliella bardawil to diabetic patients affected a significant reduction in LDL susceptibility to oxidation, as exhibited by increased lag time and reduction in malondialdehye (MDA) and lipid peroxides (PD). Secondly, Levy (W) teaches a method for reducing the susceptibility of LDL to lipid peroxidation comprising orally administering an effective amount of an extract derived from Dunaliella bardawil to healthy patients. For example, Levy (V) teaches that ingestion of a stereoisomeric mixture of 9-cis and all-trans betacarotene derived from the alga Dunaliella bardawil caused a 1.8-fold carotene elevation in plasma and that oxidation modification of LDL, measured for both dosage intakes, was reduced. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to use the method for treating diabetes taught by Levy (U) to provide a method for treating atherosclerosis because Levy (U) teaches, "Increased susceptibility to oxidation of LDDL derived from patients with diabetes mellitus is associated with abnormal LDL lipid composition and antioxidant content. Natural beta-carotene dietary supplementation normalizes the enhanced LDL oxidation and consequently may be of importance in delaying accelerated development of atherosclerosis in these patients", and, Levy (W) suggests, "Supplementation of beta-carotene may be an important approach to reducing atherosclerosis via its inhibitory effect on the formation of atherogenic oxidized LDL." Thus, as each of Levy (U) and Levy (W) teach that the oral administration of effective amounts of an extract derived from Dunaliella bardawil to a either a diabetic patient or a healthy patient have the beneficial functional inhibitory effect on the susceptibility of LDL to oxidative modification, one of ordinary skill in the art would have been further motivated and one would have had a reasonable expectation of success to modify the referenced methods by adjusting the dose amounts of the referenced extracts to provide a method for treating atherosclerosis because Levy (U) teaches that dietary supplementation of a natural isomer mixture of beta-carotene derived from an extract of Dunaliella bardawil delays oxidation of LDL derived from patients with mellitus; and, Levy (W) similarly teaches that dietary supplementation of the same algal extract taught by Levy (U) delays oxidation of LDL in healthy

> patients and "Atherogenesis involves oxidative modification of low-density lipoprotein (LDL), which is associated with the depletion of the LDL endogenous oxidants."
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> As each of the references indicate that the various proportions and amounts of the ingredients used in the claimed method of treatment are result variables, they would have been routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by each of the references.

Applicants respectfully traverse this rejection. To establish a *prima facie* case, the PTO must satisfy three requirements. First, the prior art reference must teach or suggest all the limitations of the claims. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Second, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Third, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

Both of the Levy articles are based on the hypothesis that "atherogenesis involves oxidative modification of LDL, which is associated with the depletion of the LDL endogenous anti-oxidants", and that "enrichment of LDL with the anti-oxidant β-carotene has

the potential of reducing the susceptibility of LDL to lipid peroxidation" (Levy (W), abstract). In other words, LDL is protected against oxidation by anti-oxidants, and the β-carotene contained in *Dunaliella* acts as an anti-oxidant (Levy (W), pg. 13, last paragraph).

Levy (W) was published in 1995 and concludes that β-carotene prevents artherogenesis by acting as an anti-oxidant (abstract, last 2 sentences; discussion, 1st paragraph). Levy (U) was published in 2000 and concludes that β-carotene normalizes enhanced LDL-oxidation and therefore suggests a therapeutic role to different antioxidants in diabetes (abstract, *conclusions;* page 59, last paragraph).

However, in recent years, and certainly by the filing date of the application, this hypothesis had been proven to be in error. Applicants enclose a Rule 132 Declaration by the senior author of the Levy articles, Ami Ben-Amotz, as well as a number of articles describing studies carried out which disprove the above hypothesis.

Paragraph no. 8 of the Ben-Amotz Declaration refers to Yusuf, S. et al, *Vitamin E supplementation and cardiovascular events in high-risk patients,* New England Journal of Medicine (2000) 342:154-60 [Annex B], and to Hegele, R.A., *ACE inhibition in the secondary prevention of vascular disease: the Heart Outcomes Prevention Evaluation (HOPE) trial and its substudies,* Current Atherosclerosis Reports (2000) 2:361-362 [Annex C], which both

describe the results of a large scale (over 9000 patients) clinical study of patients at high risk for cardiovascular events because they had cardiovascular disease or diabetes in addition to one other risk factor. Selected patients were treated for 4.5 years with vitamin E, a known anti-oxidant (see annex A, pg. 154, bottom of left column). The study concluded that vitamin E had no apparent effect on cardiovascular outcomes (Annex B, abstract, *conclusions;* Annex C, *discussion*).

Paragraph no. 9 of the Ben-Amotz Declaration refers to Kritharides, L. and Stocker, R., *The use of antioxidant supplements in coronary heart disease,* Atherosclerosis (2002) 164:211-219 [Annex D]. This is a review article which concludes that although in the past, various studies have been interpreted as supporting a role for antioxidants in the prevention of coronary heart disease (CHD), "supplements of α-tocopherol and β-carotene cannot be recommended for the treatment or prevention of CHD" (abstract).

Paragraph no. 10 of the Ben-Amotz Declaration refers to Zureik, M. et al, *Effects of long-term daily low-dose supplementation with antioxidant vitamins and minerals on structure and function of large arteries,* Arterioscler. Thromb. Vasc. Biol. (2004) 24:1485-1491 [Annex E], which describes the results of a study carried out on 1162 subjects in France during a period of 7.5 years. The anti-oxidants taken by the subjects included β-carotene. The conclusion reached was that of "no beneficial effects of

long-term daily low-dose supplementation of antioxidant vitamins and minerals on carotid atherosclerosis and arterial stiffness" (abstract, *conclusion*).

In summary, at the date of the filing of the application (September, 2003), one of ordinary skill in the art would have disregarded Levy (U) and Levy (W) as being outdated and shown to be in error as to the efficacy of treating diabetes mellitus and atherosclerosis with crude *Dunaliella* powder whose active ingredient is β-carotene. The present invention is thus surprising and unexpected in showing that the β-carotene contained in *Dunaliella* powder differs from the β-carotene used in the aforementioned studies, and the invention is therefore patentable over the cited art.

B. The Office Action rejects claims 1 and 3-10 under 35 U.S.C. §103(a) as being unpatentable over Levy, et al. (U) in view of Beck, (A), Pan et al. (B), Heyman, et al. (D) and Smith (N). As the basis for this rejection, the Office states:

> Applicant further claims a method according to claim 1, wherein said crude Dunaliella powder is administered together with one or more activators of nuclear receptors. Applicant further claims the method of claim 3, wherein the activators of nuclear receptors are peroxisome proliferator-activated receptor α or γ (PPARα or PPARγ) agonists. Applicant further claims the method according to claim 4, wherein the PPARα or PPARγ agonists are selected from fibrates and thiazolidinediones. Applicant further claims the method according to Claim 5, wherein the fibrates are selected from clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate and gemfibrozil. Applicant further claims the method

according to Claim 5, wherein the thiazolidinediones are selected from AVANDIA ™, troglitazone, BRL 49653, pioglitazone, ciglitazone, WAY120,744, englitazone, AD 5075, darglitazone and rosiglitazone.

The teachings of Levy are set forth above. Levy teaches the claimed method for treating diabetes mellitus except for the instantly claimed ingredients. However, it would have been obvious to one of ordinary skill in the art to add either fibrates, thiazolidinediones or a combination thereof to the method of treating diabetes mellitus taught by Levy to provide the instantly claimed method of disease treatment because at the time the invention was made the instantly claimed ingredients were known in the art for their beneficial functional effect to treat diabetes mellitus. Firstly, Beck teaches a method for the treatment of normolipidaemic diabetes mellitus comprising orally administering an effective amount of bezafibrate. Secondly, Pan teaches a method of reducing the risk of or treating diabetes mellitus comprising administering an effective amount of an antihyperlipoproteinemic agent, e.g., fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate and clinofibrate in combination with a cholesterol lowering drug, ACE inhibitor, in Column 9, lines 32-58. For example, in Column 15, line 58 to Column 16, line 2, Pan teaches administering gemfibrozil capsules either alone in combination with a cholesterol lowering drug, ACE inhibitor in the treatment of diabetes mellitus. Thirdly, Heyman teaches a method of treating diabetes mellitus comprising administering an effective amount of a thiazolidinedione, e.g., troglitazone, BRL 49653 , pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, and darglitazone, in combination with an RXR agonist to a subject. Fourthly, Smith teaches a method of treating diabetes mellitus comprising administering rosiglitazone. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the instantly claimed ingredients to the method for treating diabetes mellitus taught by Levy to provide the claimed method of treatment because Beck teaches that the oral administration of bezafibrate reduces the insulin level in normolipidaemic patients suffering from diabetes mellitus; Pan teaches that his method reduces or prevents the onset of diabetes mellitus and the onset of atherosclerosis in mammals, in Column 4, lines 27-34;

and, in Column, 2, lines 5-11, Heyman teaches that the combination of an RXR agonist and a PPARγ agonist, i.e., a thiazolidinedione, achieves synergistic action of the RXR/ PPARγ heterodimers so as to enhance adipogenic and antidiabetic effects of PPARγ; and, Smith teaches that his method for treating diabetes mellitus comprising administering rosiglitazone provides a beneficial effect on glycaemic control, on page 1, lines 19-22.

Moreover, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the instant ingredients for their known benefit since each is well known in the art for their claimed purpose and for the following reasons. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, In re Sussman, 1943 C.D. 518. Applicants invention may be predicated on an unexpected result, which typically involves synergism, an unpredictable phenomenon, highly dependent upon specific proportions and/or amounts of particular ingredients. Any mixture of the components embraced by the claims, which does not exhibit an unexpected result (e.g., synergism) is therefore ipso facto unpatentable.

Accordingly, the instant claims, in the range of proportions where no unexpected results are observed, would have been obvious to one of ordinary skill having the above-cited references before him.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants respectfully traverse this rejection. Levy, et al. (U) and Levy, et al. (W) have been discussed above. Applicants further provide a second Rule 132 Declaration by one of the

inventors, Aviv Shaish, which provides further experimental results showing that the combination of *Dunaliella* powder together with a PPARγ agonist (rosiglitazone) provides an unexpected improvement in the treatment of diabetes as opposed to the results with either component alone. In view of the fact that one of ordinary skill in the art would disregard the Levy references, and in view of the results provided in the Shaish Declaration, it is respectfully submitted that the claims are patentable over the cited art.

C. The Office Action rejects claims 1 and 8-10 under 35 U.S.C. §103(a) as being unpatentable over Levy, et al. (U) and Levy, et al. (W) in view of Pan, et al. (B), Craig, et al. (P) and Druzgala, et al. (E). As the basis for this rejection, the Office states:

> The combined teachings of Levy (U) and Levy (W) were set forth above. The combined teachings of Levy (U) and Levy (W) teach the claimed method for treating diabetes mellitus except for the instantly claimed ingredients. However, it would have been obvious to one of ordinary skill in the art to add either fibrates, thiazolidinediones or a combination thereof to the method of treating diabetes mellitus and atherosclerosis taught by the combined teachings of Levy (U and W) to provide the instantly claimed method of disease treatment because at the time the invention was made the instantly claimed ingredients were known in the art for their beneficial functional effect to treat disease conditions such as the claim-designated disease conditions, evidenced by the teachings of Pan, Craig and Druzgala. Firstly, Pan teaches a method of reducing the risk of or treating diabetes mellitus comprising administering an effective amount of an anti hyped ipoproteinemic agent, e.g., fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate and clinofibrate in combination with a cholesterol lowering drug, ACE inhibitor, in Column 9, lines 32-58. For example, in Column 15, line 58 to Column 16, line 2, Pan teaches administering gemfibrozil

capsules either alone in combination with a cholesterol lowering drug, ACE inhibitor in the treatment of diabetes mellitus. In Column 4, lines 27-34, Pan further teaches that the ingredients of his invention prevent the onset of coronary artery disease and prevent the onset of atherosclerosis in mammalian species. Secondly, Craig teaches a method of treating diabetes mellitus and diabetes mellitus related disease conditions, e.g., atherosclerosis, comprising administering rosiglitazone. Thirdly, Druzgala teaches methods of treating disorders, such as diabetes, atherosclerosis, hypercholesterolemia, and hyperlipidemia, comprising the administration of a therapeutically effective amount of a thiazaolidinedione, i.e., troglitazone (for example, REZULIN), pioglitazone, and rosiglitazone. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the instantly claimed ingredients to the method for treating diabetes mellitus taught by the combined teachings of Levy (U and W) to provide the claimed method of treatment because Pan teaches that his method reduces or prevents the onset of diabetes mellitus and the onset of atherosclerosis in mammals, in Column 4, lines 2734; and, Craig and Druzgala teach that thiazolidinediones are suitable for the treatment diabetes, atherosclerosis, hypercholesterolemia, and hyperlipidemia.

Moreover, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the instant ingredients for their known benefit since each is well known in the art for their claimed purpose and for the following reasons. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, In re Sussman, 1943 C.D. 518. Applicants invention may be predicated on an unexpected result, which typically involves synergism, an unpredictable phenomenon, highly dependent upon specific proportions and/or amounts of particular ingredients. Any mixture of the components embraced by the claims, which does not exhibit an unexpected result (e.g., synergism) is therefore ipso facto unpatentable.

> Accordingly, the instant claims, in the range of proportions where no unexpected results are observed, would have been obvious to one of ordinary skill having the above-cited references before him.
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> From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants respectfully traverse this rejection. Levy (U) and Levy (W) have been discussed above. For the reasons discussed immediately in relation to the Rule 132 Declaration by inventor Shaish, the further experimental results showing that the combination of *Dunaliella* powder together with a PPARγ agonist (rosiglitazone) provides an unexpected improvement in the treatment of diabetes as opposed to the results with either component alone. In view of the fact that one of ordinary skill in the art would disregard the Levy references, and in view of the results provided in the Shaish Declaration, it is respectfully submitted that the claims are patentable over the cited art.

D. The Office Action rejects claims 2 and 16-18 under 35 U.S.C. §103(a) as being unpatentable over Takahashi et al. (V) in view of Levy et al. (U). As the basis for this rejection, the Office states:

> Applicant further claims the method according to Claim 2, wherein said powder is encapsulated.

> The teachings of Takahashi were set forth above. Takahashi teaches the claimdesignated methods except for wherein the powder is encapsulated. However, it would have been obvious to one of ordinary skill in the art to modify the method of disease treatment taught by Takahashi by administering the reference powdered extract of Dunaliella bardawil in an encapsulated form to provide the claimed invention because at the time the invention was made it was known in the art of pharmacy that the oral administration of the claim-designated algal composition in an encapsulated form was conventional, as evidenced by the teachings of Levy set forth above. At the time the invention was made, one of ordinary skill in the would have been motivated and one would have a reasonable expectation of success to modify the method of treatment taught by Takahashi by administering the reference powdered extract of Dunaliella bardawil in an encapsulated form to provide the claimed invention because Levy teaches that the oral administration of Dunaliella bardawil provides a mean of delivering the therapeutic algal composition. Thus, the claimed invention would have been merely a matter of judicial selection to one practicing the invention to pick and choose the form for the oral administration of the referenced algal compositions to effect a result variable for the treatment of the claim-designated disease conditions, since at the time the invention was made Takahashi teaches that the oral administration of effective amounts of a powdered extract of Dunaliella had therapeutic effects for the claim-designated disease condition, and given that Levy teaches that the encapsulation of a powdered extract of the claim-designated algal extract has therapeutic beneficial effects.

Applicants respectfully traverse this rejection. For the reasons discussed above, neither Takahashi nor Levy (U), alone or in combination, teach or suggest the inventive subject matter.

E. The Office Action rejects claims 2 and 11-18 under 35 U.S.C. §103(a) as being unpatentable over Takahashi et al. (V) and Levy et al. (U) in view of Beck (A), Criere, et al. (O), Clark, et

al. (C) and Heyman, et al. (D). As the basis for this rejection, the Office states:

> Applicant further claims a method according to claim 1, wherein said crude Dunaliella powder is administered together with one or more activators of nuclear receptors. Applicant further claims the method of claim 3, wherein the activators of nuclear receptors are peroxisome proliferator-activated receptor α or γ (PPARα or PPARγ) agonists. Applicant further claims the method according to claim 4, wherein the PPARα or PPARγ agonists are selected from fibrates and thiazolidinediones. Applicant further claims the method according to Claim 5, wherein the fibrates are selected from clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate and gemfibrozil. Applicant further claims the method according to Claim 5, wherein the thiazolidinediones are selected from AVANDIA ™, troglitazone, BRL 49653, pioglitazone, ciglitazone, WAY120,744, englitazone, AD 5075, darglitazone and rosiglitazone.
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> The combined teachings of Takahashi and Levy were set forth above. The combined teachings of Takahashi and Levy teach the claimed invention except for the instantly claimed ingredients. However, it would have been obvious to one of ordinary skill in the art to add the instantly claimed ingredients to the methods for reducing triglycerides and/or increasing HDL cholesterol levels in the plasma of subject taught by the combined teachings of Takahashi and Levy to provide the claimed method of treatment because at the time the invention was made fibrates and thiazolidinediones were known in the art for their beneficial effect for treating the claim-designated disease conditions. Firstly, in Column 1, lines 11-16, Beck teaches that the administration of bezafibrate is widely used for the treatment of hyperlipidaemias (hypertriglyceride-ciaias and hypercholesterolaemias); Criere teaches a method of treating hyperlipemia, including hypercholesterolemia and hypertriglyceridemia, comprising the administration of an effective amount of fenofibrate; and Clark suggests that the administration of clofibrate, gemfibrozil, fenofibrate and bezafibrate reduce serum cholesterol. Secondly, Heyman teaches a method of treating hypertriglyceridemia comprising administering an effective amount of a thiazolidinedione, e.g., troglitazone, BRL 49653, pioglitazone, ciglitazone,

> WAY-120,744, englitazone, AD 5075, and darglitazone, in combination with an RXR agonist to a subject. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the instantly claimed ingredients to the methods for reducing triglycerides and/or increasing HDL cholesterol levels in the plasma of subject taught by the combined teachings of Takahashi and Levy to provide the claimed method of treatment because Criere, Beck and Clark teach that the claim-designated fibrates are effective in lowering serum cholesterol; and, in Column, 2, lines 5-11, Heyman teaches that the combination of an RXR agonist and a PPARγ agonist, i.e., a thiazolidinedione, achieves synergistic action of the RXR/ PPARγ heterodimers so as to enhance adipogenic and antidiabetic effects of PPARγ.
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> Moreover, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the instant ingredients for their known benefit since each is well known in the art for their claimed purpose and for the following reasons. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, In re Sussman, 1943 C.D. 518. Applicants invention is predicated on an unexpected result, which typically involves synergism, an unpredictable phenomenon, highly dependent upon specific proportions and/or amounts of particular ingredients. Any mixture of the components embraced by the claims, which does not exhibit an unexpected result (e.g., synergism) is therefore ipso facto unpatentable.
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> Accordingly, the instant claims, in the range of proportions where no unexpected results are observed, would have been obvious to one of ordinary skill having the above-cited references before him.

Applicants respectfully traverse this rejection. For the reasons discussed above, neither Takahashi nor Levy (U), alone or in combination, teach or suggest the inventive subject matter. The Beck, Criere, Heyman and Clark references do not remedy the

deficiencies of Takahashi and Levy (U).

F. The Office Action rejects claims 2 and 16-18 under 35 U.S.C. §103(a) as being unpatentable over Itoh et al. (X) in view of Takahashi et al. (V) and Levy et al. (U). As the basis for this rejection, the Office states:

> Itoh teaches a method for reducing triglycerides and cholesterol levels in the plasma of hyperlipidemic rats comprising administrating to the subject an effective amount of an extract obtained from Dunaliella bardawil. Itoh teaches, "Dunaliella, β-carotene lowered the plasma total cholesterol (TC), triglycerides (TG), LDL-cholesterol (LDL), phospholipids (PL), and free cholesterol (FC) levels of rats in both steps of lipid formation and excretion phase. Anti-lipididemic effect of Dunaliella β-carotene in lipid formation (TC, TG, PL, and FC) was remarkably higher than that in lipid excretion and depended on the dose of Dunaliella β-carotene."
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> The teachings of Itoh were set forth above. Itoh does not teach a method for reducing triglycerides comprising administering the claim-designated algal extract in the form of a crude powder and wherein the crude powder is encapsulated. However, it would have been obvious to one of ordinary skill in the art to modify the method of disease treatment taught by Itoh by administering the reference powdered extract of Dunaliella bardawil in an encapsulated powdered form to provide the claimed invention because at the time the invention was made it was known in the art of pharmacy that the oral administration of the claim-designated algal composition as a powder and as a powder in an encapsulated form was conventional, as evidenced by the teachings of Takahashi and Levy set forth above. At the time the invention was made, one of ordinary skill in the would have been motivated and one would have a reasonable expectation of success to modify the method of treatment taught by Itoh by administering the reference powder extract of Dunaliella bardawil in an encapsulated form to provide the claimed invention because Takahashi teaches that the administration of an effective amount of a powder extract of Dunaliella bardawil to hypercholesterolemic mice significantly decreased the

> levels of plasma total cholesterol and LDL-cholesterol and Levy teaches that the oral administration of Dunaliella bardawil provides a mean of delivering the therapeutic algal composition. Thus, the claimed invention would have been merely a matter of judicial selection to one practicing the invention to pick and choose the form for the oral administration of the reference algal compositions to effect a result variable for the treatment of the claim-designated disease conditions, since at the time the invention was made Takahashi teaches that the oral administration of a powder extract of Dunaliella bardawil provides an antihypercholesterolemic beneficial functional effect and Levy teaches that the encapsulation of a powder extract of the claim-designated algal extract has therapeutic beneficial effects. According, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Applicants respectfully traverse this rejection. The Takahashi and Levy (U) references were discussed above. Itoh describes results obtained using β-carotene extracted from *Dunaliella bardawil*. It is clear that results obtained using extracted β-carotene do not disclose the inventive subject matter, which uses crude *Dunaliella* powder. In fact, Itoh states that the use of extracted *Dunaliella* β-carotene in rats resulted in "no remarkable changes in HDL-cholesterol". This differs from the results described in the instant specification (example I). Thus, Itoh teaches away from the invention, which claims an increase in HDL cholesterol, and certainly does not teach the invention.

G. The Office Action rejects claims 2 and 11-18 under 35 U.S.C. §103(a) as being unpatentable over Itoh, et al. (X), Takahashi, et al. (V) and Levy, et al. (U) in view of Beck (A),

Criere, et al. (O), Clark, et al. (C) and Heyman, et al. (D). As the basis for this rejection, the Office states:

> The combined teachings of Itoh, Takahashi and Levy were set forth above. The combined teachings of Itoh, Takahashi and Levy teach the claimed invention except for the instantly claimed ingredients. However, it would have been obvious to one of ordinary skill in the art to add the instantly claimed ingredients to the methods for reducing triglycerides and/or increasing HDL cholesterol levels in the plasma of subject taught by the combined teachings of Itoh, Takahashi and Levy to provide the claimed method of treatment because at the time the invention was made fibrates and thiazolidinediones were known in the art for their beneficial effect for treating the claimdesignated disease conditions. Firstly, in Column 1, lines 11-16, Beck teaches that the administration of bezafibrate is widely used for the treatment of hyperlipidaemias (hypertriglyceride-ciaias and hypercholesterolaemias); Criere teaches a method of treating hyperlipemia, including hypercholesterolemia and hypertriglyceridemia, comprising the administration of an effective amount of fenofibrate; and Clark suggests that the administration of clofibrate, gemfibrozil, fenofibrate and bezafibrate reduce serum cholesterol. Secondly, Heyman teaches a method of treating hypertriglyceridemia comprising administering an effective amount of athiazolidinedione, e.g., troglitazone, BRL 49653, pioglitazone, ciglitazone, WAY120,744, englitazone, AD 5075, and darglitazone, in combination with an RXR agonist to a subject. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the instantly claimed ingredients to the methods for reducing triglycerides and/or increasing HDL cholesterol levels in the plasma of subject taught by the combined teachings of Itoh, Takahashi and Levy to provide the claimed method of treatment because Criere, Beck and Clark teach that the claim-designated fibrates are effective in lowering serum cholesterol; and, in Column, 2, lines 5-11, Heyman teaches that the combination of an RXR agonist and a PPARγ agonist, i.e., a thiazolidinedione, achieves synergistic action of the RXR/ PPARγ heterodimers so as to enhance adipogenic and antidiabetic effects of PPARγ.

> Moreover, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the instant ingredients for their known benefit since each is well known in the art for their claimed purpose and for the following reasons. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, In re Sussman, 1943 C.D. 518. Applicants invention may be predicated on an unexpected result, which typically involves synergism, an unpredictable phenomenon, highly dependent upon specific proportions and/or amounts of particular ingredients. Any mixture of the components embraced by the claims, which does not exhibit an unexpected result (e.g., synergism) is therefore ipso facto unpatentable.
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> Accordingly, the instant claims, in the range of proportions where no unexpected results are observed, would have been obvious to one of ordinary skill having the above-cited references before him.

Applicants respectfully traverse this rejection. The Itoh, et al., Takahashi, et al., and Levy, et al. (U) references were discussed above. The Beck, Criere, Heyman and Clark references do not remedy the deficiencies of Itoh, Takahashi and Levy (U).

Further, Applicants respectfully note that the Examiner has provided no support whatsoever for the required conclusion that one of ordinary skill in the art would have been motivated to combine the cited references to reach the inventive subject matter. Thus, on this point alone, the Office Action has failed to establish a prima facie case of obviousness. In particular, the use of as many as seven references in combination is prima facie evidence of non-obviousness in the absence of any teaching or suggestion,

whatsoever, in the cited references which would have motivated one to combine the particular references cited by the Examiner.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the rejections of claims 1-18 and allow all pending claims presented herein for reconsideration. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,

NATH & ASSOCIATES PLLC

Date: October 4, 2004 By: _____

Gary M. Nath
Reg. No. 26,965
Lee C. Heiman
Reg. No. 41,827
Customer No. 20529

NATH & ASSOCIATES PLLC
1030 15th Street, N.W., 6th Floor
Washington, D.C. 20005
Tel: (202)-775-8383
Fax: (202)-775-8396
GMN:LCH ROA.wpd